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08/866,279	05/30/97	DYMECKI S	234805

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EXAMINER	
BAKER, A	

ART UNIT	PAPER NUMBER
1632	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 08/866,279	Applicant(s) Dymecki
	Examiner Anne-Marie Baker, Ph.D.	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Mar 15, 1999*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-49* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-49* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed March 15, 1999 (Paper No. 6) has been entered.

Claims 1-49 are pending in the instant application.

The following rejections are reiterated and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous Office Action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4 was rejected under 35U.S.C. 112, first paragraph, for reasons of record advanced on page 2 of the previous Office Action mailed 9/14/98 (Paper No. 4), because the specification, while being enabling for integration of Flp-recognition sequences into the genome of a mouse, does not reasonably provide enablement for introducing the Flp-recognition sequences in such a way as to generate a mosaic transgenic mouse wherein at least two diploid cells have different numbers of Flp-recognition sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant clarifies that a mosaic or chimeric transgenic mouse comprising cells that have undergone site-specific recombination between Flp-recognition sequences may differ in the number of Flp-recognition

sequences they contain because each cell may undergo a different number of Flp-mediated recombination events.

The rejection is hereby withdrawn.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 41, 42, and 47 stand rejected under 35 U.S.C. 112, second paragraph, for reasons of record advanced on page 3 of the previous Office Action (Paper No. 4) as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15 and 47 are indefinite in the recitation of the transgene or nucleic acid selected from the group consisting of a developmental gene or an essential gene. It is unclear what is meant by the term "essential gene" because it is not evident in what respect the gene is considered to be essential. The gene could be essential for the viability of the organism or essential for a particular function. Additionally, it is unclear what is meant by a "developmental gene" because such a gene could function in the control of development or could be differentially expressed in different stages of development while not playing a role in the control of development.

Claims 41 and 42 are indefinite in the recitation of a "developmental gene" for the reasons described above.

Applicant asserts that these terms are well defined in genetics. Furthermore, Applicant argues that an essential gene may be required for viability of an individual cell or organism and that a gene encoding an enzyme may be required to perform an essential function in a metabolic pathway. Applicant alleges that the

alternatives presented by the Examiner are not contradictory. However, as a matter of principle, any gene is essential for the function that it performs. Thus, an "essential gene" is not distinct from any other gene and all genes would therefore be considered essential. The term "essential gene" could refer to any gene and thus it is unclear what exactly is "essential" about one gene over any other gene. Applicant seems to be arguing that the intended meaning of the term is limited to genes that are essential for the viability of the organism. Amendment to the claim language clarifying this intended meaning would be appropriate.

Applicants argue that a "developmental gene" is one that is required to control differentiation of an individual cell or development of an organism. However, the claim language is indefinite because the term could also be interpreted to include genes that are merely differentially expressed during development, but do not play a role in the control of development. If Applicant intends for the meaning of the term to be limited to genes that function in the control differentiation, amendment to the claim language clarifying this intended meaning would be appropriate.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4-19, 22-27, 29-36, 41-43, 45, and 48 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kilby et al. (1993) for reasons of record advanced on pages 4-5 of the previous Office Action (Paper No. 4).

Applicant argues that Kilby et al. did not reduce to practice the generation and use of transgenic mice with FLP recombinase gene and FRT target sequences and that this reference does not put the public in possession of the claimed invention. However, Kilby et al. noted that site-specific recombinases would be useful in transgenic animals for applications in developmental biology, in activating or removing genes at particular stages. Furthermore, they stated that such controlled gene expression could mark a clone of cells for lineage studies, or allow the effect of lethal or deleterious sequences to be studied in a particular cell type or developmental stage (p. 417, paragraph 2). Kilby et al. suggests making exactly the transgenic animals instantly claimed. Furthermore, Kilby et al. provided all of the teachings necessary to enable one skilled in the art to make and use the transgenic mice claimed in the instant invention, including the motivation to use such animals for developmental studies, cell lineage studies, and controlled gene activation/inactivation studies in conjunction with cell-type specific gene expression.

Claims 1, 2, 4-13, 22-27, 29-33, 41-43, 45, and 48 stand rejected under 35 U.S.C. 102(b) as being anticipated by Wigley et al. (1994) for reasons of record advanced in the previous Office Action (Paper No. 4).

Applicants argue that Wigley et al. did not reduce to practice the generation and use of transgenic mice with the FLP recombinase gene and FRT target sequences and that this reference does not put the public in possession of the claimed invention. However, Wigley et al. suggest making exactly the transgenic mice instantly claimed. Furthermore, Wigley et al. provided all of the teachings necessary to enable one skilled in the art to make and use the transgenic mice claimed in the instant invention, including the motivation to use FLP-mediated recombination to excise marker genes, such as the neomycin resistance gene.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-13, 15, 22-27, 29-33, 37-43, 45, 47, and 48 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lakso et al. (1992), Wigley et al. (1994), Marx (1993), Marshall (1989), and Bieche et al. (1992) for reasons of record advanced on pages 7-9 of the previous Office Action (Paper No. 4).

Applicant argues that Lakso et al. does not teach the use of Flp recombinase in transgenic mice. However, Lakso et al. suggest that the FLP recombinase will be useful in directing precise site-specific DNA rearrangements in transgenic animals, and emphasize that the FLP recombinase of *Saccharomyces cerevisiae* has been shown to be proficient for recombination in both *Drosophila* and in cultured mammalian cells (p. 6235, paragraph 2).

Applicant argues that Wigley et al. does not suggest the use of Flp recombinase in transgenic mice because their approach describes transgenic mice generated from ES cells that have been modified by Flp-mediated recombination while in culture, and thus the Flp-mediated recombination would occur in ES cells, not in a transgenic mouse as claimed in the present invention. However, Wigley et al. state that the ES cell lines are to be transfected with a source of FLP (p. 586, last paragraph). Such an approach, which involves producing transgenic mice from the modified ES cells, would necessarily result in transgenic mice expressing FLP recombinase. Thus, although some recombination would occur in the cultured ES cells, recombination would continue to occur in the resultant transgenic mice because the FLP recombinase gene would be present and would be expressed.

Applicant argues that Cre recombinase is not analogous to Flp recombinase because the two recombinases are not identical in their enzymatic function. In support, Applicant offers the reference of Gu et al. (1993) which teaches that Flp was not as efficient as Cre in catalyzing recombination in ES cells. Sauer et al. also teach that Flp catalyzes excision less efficiently than Cre in ES cells Applicant further points to the Barinaga (1994) reference for its statement (p. 28) that Flp got a bad reputation when several groups tried to use it to make knockout mice because they had trouble getting it to work well in ES cells. However, the reference also reports that while others gave up on FLP, O'Gorman did not and has now shown that the enzyme works nicely in transgenic mice (p. 28, column 3, paragraph 3). O'Gorman says "We know FLP works [in mice]. That is absolutely clear-cut." The reference goes on to say that he believes it can be made to work in ES cells as well. Thus it was ultimately concluded that FLP works well in transgenic mice.

Applicant argues that a Flp transgenic mouse was not described in a scientific publication until 1996 when the inventor reported the generation of the mice of the invention. Applicant submits publications using the transgenic line described in the instant application and a list of investigators who have requested and received Flp-transgenic mice from the Applicant. Nevertheless, the cited prior art renders the invention obvious and neither publications describing the mice, use of the mice, nor the requests of other investigators overcome the rejection as previously advanced.

Applicant asserts that there was not a reasonable expectation of success before Applicant's publication disclosing the mice and cites a long lapse of time between publications disclosing transgenic mice with Cre and then Flp. However, as discussed in the previous Office Action and herein above, the prior art repeatedly points to the potential uses of Flp recombinase as a substitute for the Cre recombinase system, and the art cited by Applicant states that Flp works in transgenic mice.

Applicant contends that one of skill in the art would not have been motivated to combine the cited references and that the motivation stated on page 9 of the Office Action is that the combination would "generate a transgenic mouse useful for the study of neoplastic transformation, *in vivo*." Applicant argues that this merely states the result that Applicant has achieved. On the contrary, the cited art provides the motivation because Lakso et al. described the use of the Cre-lox system to activate oncogenes and Lakso et al. suggested the use of FLP recombinase in transgenic mice to do the same thing.

Claims 3, 21, 28, 44, 46, and 49 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wigley et al. (1994), Panigrahi et al. (1992), O'Gorman et al. (1991), Wahl et al. (US Pat. No. 5,654,182; 1997), Hartley et al. (1980), and Buccholz et al. (1996) for reasons of record advanced on pages 10-11 of the previous Office Action (Paper No. 4).

Wigley et al. and Applicant's arguments regarding this reference have already been addressed herein above.

Applicant argues that a reasonable expectation of success would not have been anticipated and that the reasons stated by the Examiner for an expectation of success are insufficient because results in tissue culture and in transgenic *Drosophila* cannot be so easily extrapolated to transgenic mice. Applicant does not offer any support for this assertion that such results cannot be extrapolated to transgenic mice, other than the fact that Flp transgenic mice were not made as of the date of the publication of Kilby et al. No presumption can be made from the absence of a report on Flp transgenic mice. The absence of such a publication does not indicate that an expectation of success cannot be based on other successful uses of Flp recombinase in biological systems

Applicant argues that the thermolability of Flp recombinase explains the failures of others to make the claimed invention prior to Applicant's success. Applicant appears to take the position that a lower temperature optimum for Flp relative to Cre would have presented an obstacle to the generation of the transgenic mice of the invention. Applicant points to Buccholz et al. (1996) which states that "FLP is more thermolabile having an optimum near 30°C and little detectable activity above 39°C...Cre is optimally efficient at 37°C and above." Although Buccholz et al. recommend "the use of Cre for applications in mice that require efficient recombination," the authors also point out applications for which the use of FLP would be preferable. On p. 4262 (Buccholz et al., 1996) the authors state "FLP may be particularly useful for applications that do not rely on efficiency but depend on tight regulation. For example, cell lineage studies using recombination depend on a single rare recombination event. This should be easier to accomplish with FLP rather than Cre. Similarly, in certain gain-of-function applications, such as recombinase induced cell differentiation or those that initiate tumourigenesis by recombination, FLP may be more suited to the demand for the complete absence of recombination before the chosen induction point." The temperature range reported by Buccholz et al. clearly indicates that FLP recombinase would function at physiological temperatures. The authors report on p. 4257 that "[b]etween 34 and 39C, both recombinases appeared to be fully active." Despite Applicant's belief that FLP thermolability would be expected to hamper its function in transgenic mice, it is unclear what steps Applicant was required to take to overcome this putative barrier (Flp thermolability) to making the Flp recombinase transgenic mice of the invention.

Applicant argues that the stated motivation to combine the cited references "to generate a transgenic mouse useful for *in vivo* genetic manipulation" merely states the result that Applicant has achieved. In fact, the cited art demonstrates the use of Cre recombinase for in vivo genetic manipulation and numerous references have been cited that suggest the substitution of FLP recombinase for the same purpose.

Claims 1, 12, 15, 20, 24, 43, and 47 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Orban et al. (1992) and Wigley et al. (1994) for reasons of record advanced on pages 11-14 of the previous Office Action (Paper No. 4).

Applicant argues that there was no reasonable expectation of success when the present invention was made because of the different levels of recombinase activity for Cre and Flp. This argument has already been addressed herein above.

Applicant contends that there was a long-felt need for a transgenic mouse with a functional Flp transgene, that others had failed in their attempts to produce these mice, and that the list of 33 investigators who have requested the mice of the invention supports Applicant's contention of a long-felt need. Nevertheless, the cited prior art renders the invention obvious and the requests of other investigators for the mice of the invention does not overcome the rejection as previously advanced. Applicant is invited to submit evidence of the failed attempts of others to produce the mice of the invention.

Conclusion

No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and

any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Friday from 8:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton, can be reached on (703) 308-2801. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne-Marie Baker, Ph.D.

Bruce Campell

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800